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HEAT EXCHANGE THROUGH CUTANEOUS VASODILATION AFTER ATROPINE TREATMENT IN TWO ENVIRONMENTS

U S ARMY RESEARCH INSTITUTE
OF
ENVIRONMENTAL MEDICINE
Natick, Massachusetts

OCTOBER 1987

UNITED STATES ARMY
MEDICAL RESEARCH & DEVELOPMENT COMMAND

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(U) This report summarizes two tightly controlled laboratory studies in which the thermoregulatory effects of an intramuscular injection of atropine sulfate (2 mg) were compared with a placebo injection of sterile saline during two environmental conditions. Four subjects were tested in each environmental condition (22°C or 30°C) during seated cycle exercise at a moderate exercise intensity (55% $\dot{V}O_2$ peak). Esophageal temperature (T_{es}), mean weighted skin temperature (T_{sk}), and forearm sweating rate ($\dot{m}_s$) were continuously measured during 30 minutes of rest and 35 minutes of exercise. Skin blood flow (FBF) from the forearm was measured twice each minute by venous occlusion plethysmography. The expected decrease in whole body and local sweating rate (-60%) occurred in both environments in the atropine treated subjects. During exercise, FBF was 85% greater at 30°C and 95% greater at 22°C after treatment. The increased skin blood flow compensated for the suppression in sweating increasing dry heat loss in the atropine experiments. At 22°C, core temperature actually decreased 0.2°C in the atropine treated subjects during exercise as a result of

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enhanced dry heat exchange. The atropine-induced vasodilation, based on regression analysis of the FBF:T_{es} relationship during changing T_{es} was due to an elevated slope (27.7 vs 15.0 at 30°C; 8.1 vs 2.3 at 22°C) with an unchanged T_{es} threshold for vasodilatory onset. The T_{es} for onset of $\dot{m}_s$ was increased 0.3°C at both 22 and 30°C by the atropine treatment, with no change in the slope of the regression equation. The atropine-induced vasodilation was widespread as skin temperatures increased at all sites measured. These results suggest that the peripheral modification of cutaneous blood flow which occurs in atropine treated subjects is sufficient to alter heat exchange in both warm and cool environments.

The views, opinions, and/or findings contained in this report are those of the authors and should not be contrued as an official Department of the Army position, policy or decision unless so designated by other official documentation.

Human subjects participated in these studies after giving their informed voluntary consent. Investigators adhered to AR 70-25 and USAMRDC Regulation 70-25 on Use of Volunteers in Research.

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ACKNOWLEDGEMENTS

The authors acknowledge the expertise of T.J. Doherty in data collection and statistical programming, the assistance provided by Drs. A.E. Allan, P.B. Rock, R.R. Gonzalez and S.P. Bruttig and Mr. B.S. Cadarette during the experiments.

Heat exchange through cutaneous vasodilation after atropine treatment in two environments

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October 1987

PREFACE

The methodology and findings of these studies as described and referenced in this report have been submitted to the open literature as follows:

Kolka, M.A. and L.A. Stephenson. Cutaneous blood flow and local sweating after atropine administration. Pflugers Archiv. (in press).

Kolka, M.A., L.A. Stephenson, A.E. Allan and P.B. Rock. Atropine-induced cutaneous vasodilation decreases core temperature during exercise. J. Appl. Physiol. (in review).

Kolka, M.A., L.A. Stephenson, S.P. Bruttig, B.S. Cadarette and R.R. Gonzalez. Human thermoregulation after atropine and/or pralidoxime administration. Aviat. Space and Environmental Medicine 58:545-549, 1987.

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ABSTRACT

This report summarizes two tightly controlled laboratory studies in which the thermoregulatory effects of an intramuscular injection of atropine sulfate (2 mg) were compared with a placebo injection of sterile saline during two environmental conditions. Four subjects were tested in each environmental condition (22°C or 30°C) during seated cycle exercise at a moderate exercise intensity (55% $\dot{V}_{O2}$ peak). Esophageal temperature (T_{es}), mean weighted skin temperature ($\bar{T}_{sk}$), and forearm sweating rate ($\dot{m}_s$) were continuously measured during 30 minutes of rest and 35 minutes of exercise. Skin blood flow (FBF) from the forearm was measured twice each minute by venous occlusion plethysmography. The expected decrease in whole body and local sweating rate (-60%) occurred in both environments in the atropine treated subjects. During exercise, FBF was 85% greater at 30°C and 95% greater at 22°C after atropine treatment. The increased skin blood flow compensated for the suppression in sweating increasing dry heat loss in the atropine experiments. At 22°C, core temperature actually decreased 0.2°C in the atropine treated subjects during exercise as a result of enhanced dry heat exchange. The atropine-induced vasodilation, based on regression analysis of the FBF:T_{es} relationship during changing T_{es} was due to an elevated slope (27.7 vs 15.0 at 30°C; 8.8 vs 2.3 at 22°C) with an unchanged T_{es} threshold for vasodilatory onset. The T_{es} for onset of $\dot{m}_s$ was increased 0.3°C at both 22 and 30°C by the atropine treatment, with no change in the slope of the regression equation. The atropine-induced vasodilation was widespread as skin temperatures increased at all sites measured. These results suggest that the peripheral modification of cutaneous blood flow which occurs in atropine treated subjects is sufficient to alter heat exchange in both warm and cool environments.

INTRODUCTION

The anticholinergic effect of systemic atropine treatment on the eccrine sweat gland is well known and the inhibition of sweat secretion during exercise and heat stress is well documented in the scientific literature (1, 2, 7, 8, 10, 11, 13). We have consistently observed a 45 to 65% decrease in evaporative heat loss through the inhibition of sweat secretion during exercise in the heat following systemic atropine treatment (7, 8, 10, 11, 13).

The intramuscular injection of small doses of atropine sulfate (2 mg) is associated with widespread cutaneous vasodilation appearing thirty to forty-five minutes after treatment (10, 11). We have reported a decreased dry heat gain in hot environments associated with this increased cutaneous vasodilation (7,8). These observations indicated that atropine altered the thermal gradient from the body surface to the environment and implied that excessive dry heat loss would occur in a cooler environment. In the current report, the cutaneous blood flow response was estimated by venous occlusion plethysmography, rather than calculated as changes in dry heat loss from the heat balance equation. Particular attention was given to the change in cutaneous perfusion during times when core temperature was changing in order to evaluate the vasomotor effector response.

Military Relevance

Current U.S. Army doctrine instructs soldiers to self-administer atropine when exposed to organophosphate poisoning; however, it is possible that atropine could be used in the absence of a nerve agent challenge. In our past evaluations, we have consistently shown atropine was a cutaneous vasodilator which significantly altered heat

exchange in warm to hot environments. Recently, the combined challenge of atropine and pralidoxime was evaluated with similar vasodilatory effects as atropine administered singularly. Consequently, the problems associated with heat exchange in warm and cool environments after antidote administration can be adequately addressed by using atropine alone and eliminating the subjects' exposure to any more risk than absolutely necessary (i.e., treatment with pralidoxime also). The regulation of body temperature in a cool environment may be compromised with the enhanced heat loss associated with atropine-induced cutaneous vasodilation. This evaluation will provide information which will aid our predictive efforts on soldier performance following pre-treatment or treatment drug administration.

Minimizing risks to subjects

With the exception of the administration of atropine, all of the procedures in these studies fell within the framework, restrictions and safety limitations of the Type Protocols for Human Research Studies Thermal Stress and Exercise and Physical Training March 1984.[1] To minimize risks associated with atropine, volunteers were given medical examinations prior to acceptance as subjects. No one with a history of asthma, glaucoma or intraocular injury, peptic ulcer, or adverse reactions to previous atropine administration (as in the form of eye drops, antispasmotics or decongestants) was used as a subject. Fatalities from atropine alone are rare; the lethal dose is unknown (it may be as low as 65 mg for some individuals, or greater than 1000 mg for others). Central nervous system manifestations (emotional instability, anxiety,

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1./ Approved 5 March 1984. The type protocol provides information and explanations about conditions, standards and safeguards, in order to serve as an encompassing framework for specific in-house studies in its general subject area. It is to be used as a reference to facilitate the understanding and review of specific study protocols which conform to its provisions, and thus do not exceed the degree of risk, and safety limits herein stipulated (reference para 19, USAMRDC Reg 70-25, 27 April 1981).

hallucinations) are usually mild or not seen with less than a 5 mg dose. Fatigue, headache, lightheadedness and non-coordinated movement can be expected in at least 25% of subjects receiving a 2 mg dose (4).

METHODS

Eight healthy male subjects were evaluated during seated cycle exercise in one of two environmental temperatures (n=4 per environment). All experimental procedures were identical with two exceptions; subjects were exposed to either 22°C or 30°C (ambient water vapor pressure = 1.0 kPa in both environments), and within a specific environment the subjects were studied on one occasion after 2 mg atropine sulfate (Elkins-Sinn, Cherry Hill, NJ) was injected into the vastis lateralis and once following a sterile saline placebo, injected in an identical manner. Subjects were not informed of the drug being injected and treatment order (drug or placebo) was counterbalanced. All procedures had been approved by the local human review committee.

The subject reported to the environmental chamber having not eaten for the previous twelve hours. He was weighed and then sat in a chair placed behind the pedals of a cycle ergometer, such that when pedalling his legs would be parallel to the floor. He swallowed an esophageal catheter containing a copper-constantan thermocouple and adjusted it to heart level for the measurement of esophageal temperature (T_{es}). Eight surface thermocouples (copper-constantan) were placed on the skin to estimate a mean weighted (12) skin temperature ($\bar{T}_{sk}$). Local sweating rate ($\dot{m}_s$) was measured from the left forearm with a small dew-point sensor (5, 9). Skin blood flow (FBF) was measured from the right forearm by venous occlusion plethysmography as described by Whitney (14) and modified by Hokanson (6). Whole

body sweating ($\dot{M}_s$) was determined from body weight before and after the exercise bout. Heart rate was measured from the EKG, and mean arterial pressure (MAP) was measured by an ascultatory technique and calculated as 1/3 systolic pressure and 2/3 diastolic pressure.

At this point, the physician injected the atropine or the sterile saline. On-line data collection began. Metabolic heat production was evaluated from oxygen consumption measurements made during the 35 minute rest period and during exercise. Exercise began at 55% of each subjects previously determined $\dot{V}_{O2}$ peak and continued for 30 minutes.

The experiments at 30°C were completed on subjects 1-4 in November of 1985 and were followed by the 22°C exposures in February of 1987 for subjects 5-8 (Table 1). The data were analyzed within a given ambient temperature by analysis of variance with repeated measures.

TABLE 1. SUBJECT CHARACTERISTICS

	AGE (yr)	Ht (cm)	Wt (kg)	SA (m^2)	$\dot{V}_{O2}$ peak[1] ($l \cdot min^{-1}$)	Body Fat[2] (%)
1	22	185.4	88.3	2.13	4.11	16.8
2	20	177.8	67.0	1.79	3.47	13.4
3	19	170.2	87.0	2.06	3.97	23.1
4	24	181.0	82.8	2.12	3.28	21.4
5	19	180.3	77.1	2.00	3.83	9.7
6	24	172.7	78.9	1.93	3.81	17.0
7	18	188.0	64.0	1.87	3.29	13.5
8	18	182.9	66.5	1.87	3.76	13.4
$\bar{x}$	20.5	179.8	76.5	1.97	3.69	16.0
sd	(2.5)	(6.1)	(9.6)	(0.13)	(0.31)	(4.5)

[1] Measured while seated behind the pedals of a cycle ergometer
[2] Hydrostatic weighing

RESULTS

The thermoregulatory and cardiovascular responses of the subjects at rest and during exercise in either 30°C or 22°C are presented in Tables 2 and 3. Heart rate was significantly increased during rest in 22°C and exercise in both environments ($p<0.05$) after atropine administration. During exercise in the atropine treated subjects, sweating was significantly depressed ($p<0.05$) and forearm blood flow was enhanced ($p<0.05$) in both environments. Specifically, at 30°C, both forearm sweating and whole body sweating were reduced 60%. Forearm blood flow increased 86% after atropine during steady-state exercise resulting in a 2.1°C ($p<0.05$) increase in $\bar{T}_{sk}$ compared to the control experiment. T_{es} was significantly increased during steady-state exercise after atropine administration ($p<0.05$). A typical response for esophageal temperature and forearm blood flow during rest, exercise and recovery from exercise at 30°C is shown in Figures 1 and 2 for a representative subject. In the cooler environment, body temperature actually decreased during exercise in the atropine experiment resulting from the increased dry heat loss, as shown in Figure 3 for a representative subject. The forearm blood flow response for a representative subject is presented in Figure 4 during rest and exercise at 20°C. Forearm blood flow continued to increase throughout the exercise bout after atropine administration, but during the control experiment, FBF stabilized during steady-state exercise. In the experiments conducted at 20°C, whole body sweating was decreased an average of 57% and local (forearm) sweating was depressed an average of 68%. The 98% increase in forearm blood flow seen during steady-state exercise in 20°C in the atropine experiments (Table 3) resulted in a significantly higher $\bar{T}_{sk}$ (1.55°C, $p<0.05$).

TABLE 2. MEAN (± sd) TEMPERATURE PARAMETERS FOR SUBJECTS 1-4 AT REST AND DURING EXERCISE AT 30°C.

	T_{es} (°C)	$\bar{T}_{sk}$ (°C)	FBF ($ml \cdot 100ml^{-1} \cdot min^{-1}$)	$\dot{m}_s$ ($mg \cdot cm^{-2} \cdot min^{-1}$)	HR ($b \cdot min^{-1}$)	MAP [1] (torr)	$\dot{M}_s$ ($g \cdot min^{-1}$)
REST							
Saline	36.67	34.04	1.8	0.16	67	92	—
	(0.15)	(0.28)	(0.8)	(0.06)	(8)	(11)	
Atropine	36.61	34.06	1.8	0.15	59	83	—
	(0.18)	(0.30)	(0.5)	(0.04)	(13)	(5)	
EXERCISE							
Saline	37.37	33.62	9.2	1.08	130	103	13.2
	(0.15)	(0.51)	(0.4)	(0.30)	(5)	(3)	(3.7)
Atropine	37.78*	35.72*	17.1*	0.43*	158*	101	5.5*
	(0.18)	(0.49)	(5.8)	(0.14)	(4)	(13)	(1.4)

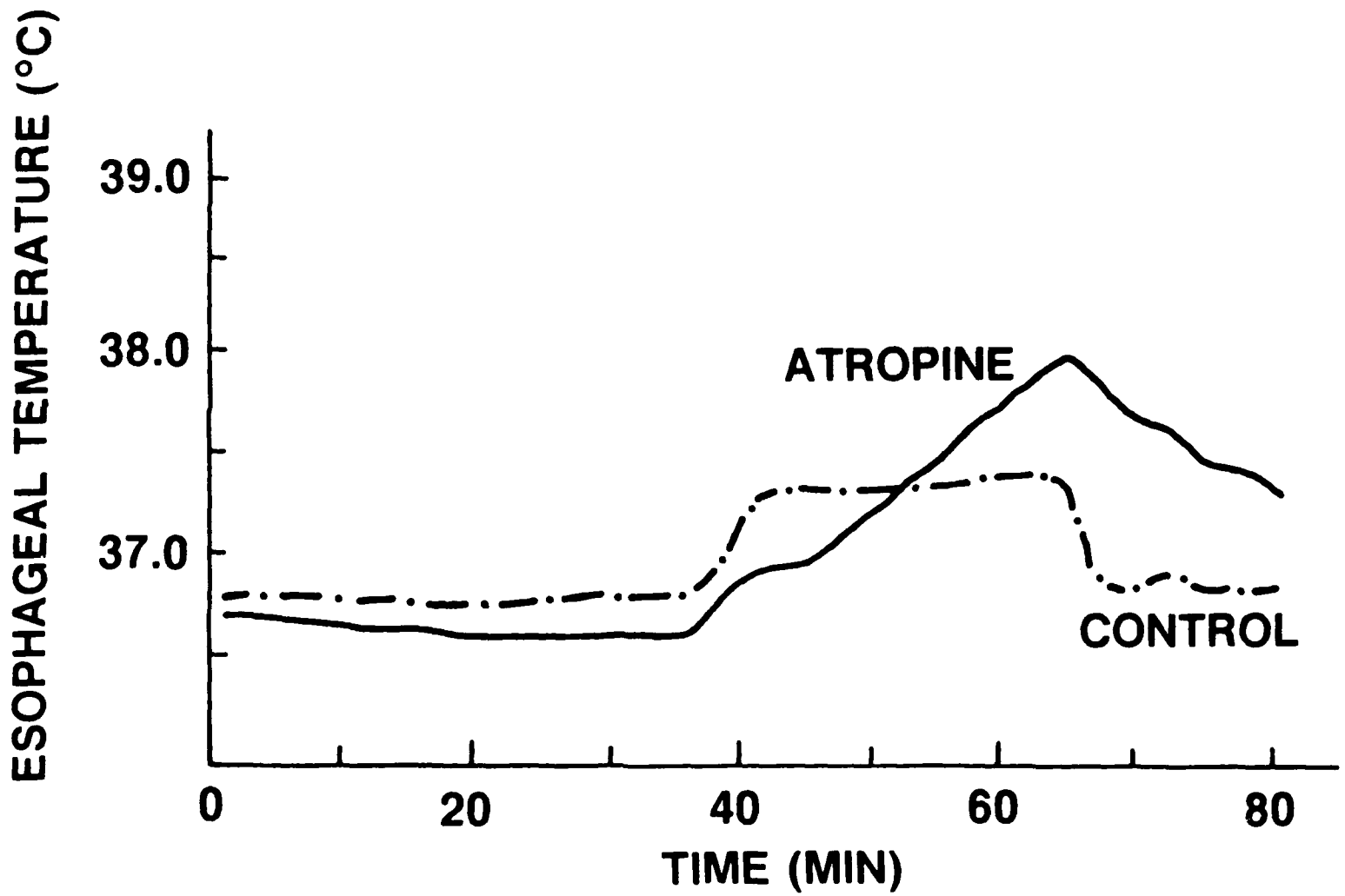
[1] MAP, mean arterial pressure

* $p < 0.05$, different from saline

TABLE 3. MEAN (± sd) TEMPERATURE PARAMETERS FOR SUBJECTS 5-8 AT REST AND DURING EXERCISE AT 22°C.

	T_{es} (°C)	$\bar{T}_{sk}$ (°C)	FBF (ml·100ml^{-1}·min^{-1})	$\dot{m}_s$ (mg·cm^{-2}·min^{-1})	HR (b·min^{-1})	$\dot{M}_s$ (g·min^{-1})
REST						
Saline	36.79 (0.20)	30.29 (0.51)	0.4 (0.1)	0.07 (0.01)	69 (18)	—
Atropine	36.81 (0.15)	30.14 (0.31)	0.4 (0.1)	0.07 (0.01)	86* (18)	—
EXERCISE						
Saline	37.36 (0.10)	31.01 (0.33)	4.1 (3.3)	0.77 (0.23)	138 (16)	9.4 (3.3)
Atropine	37.26 (0.22)	32.56* (0.87)	8.1* (3.6)	0.25 (0.17)	162* (13)	4.0* (2.7)

* $p < 0.05$, different from saline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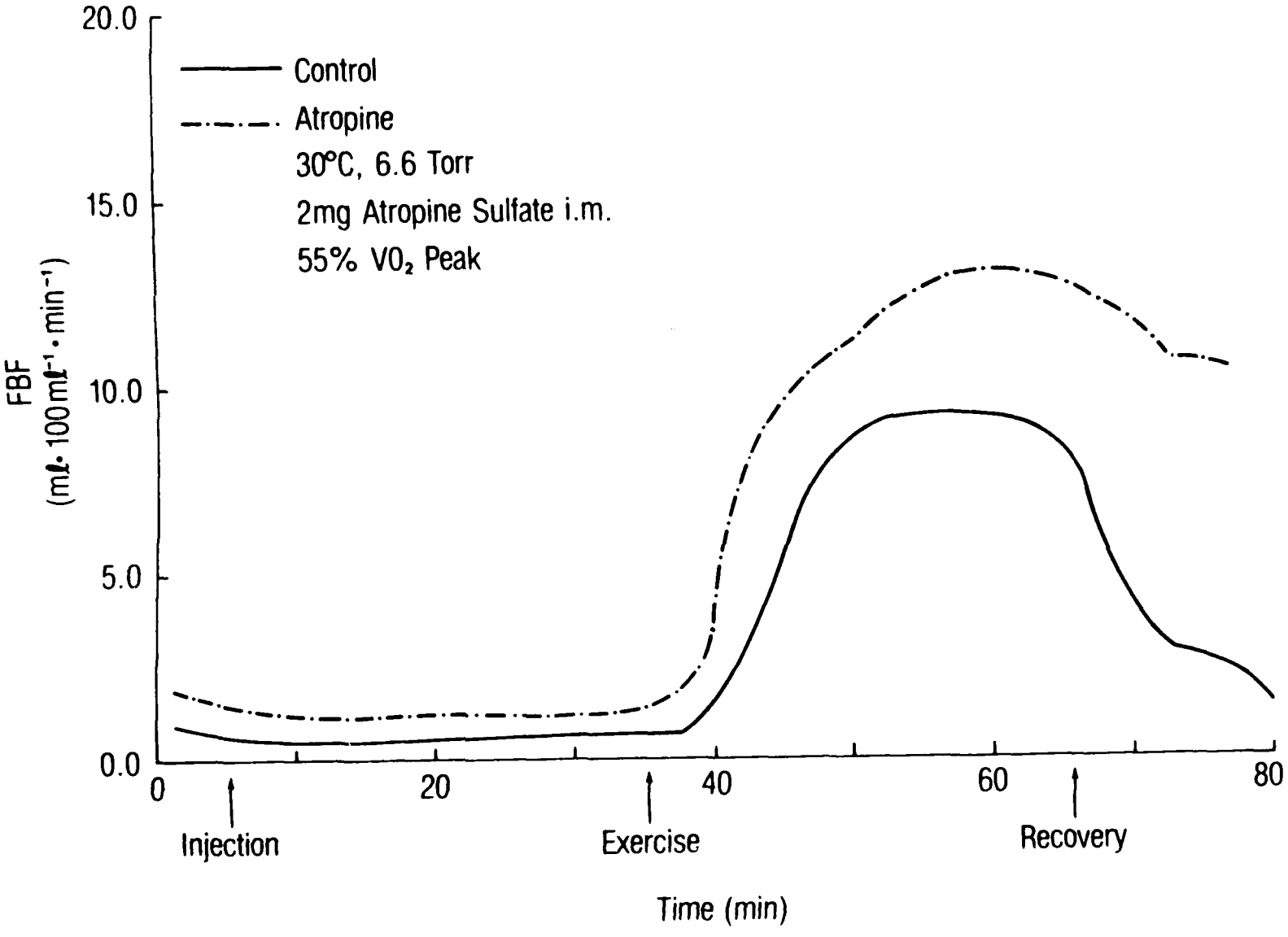
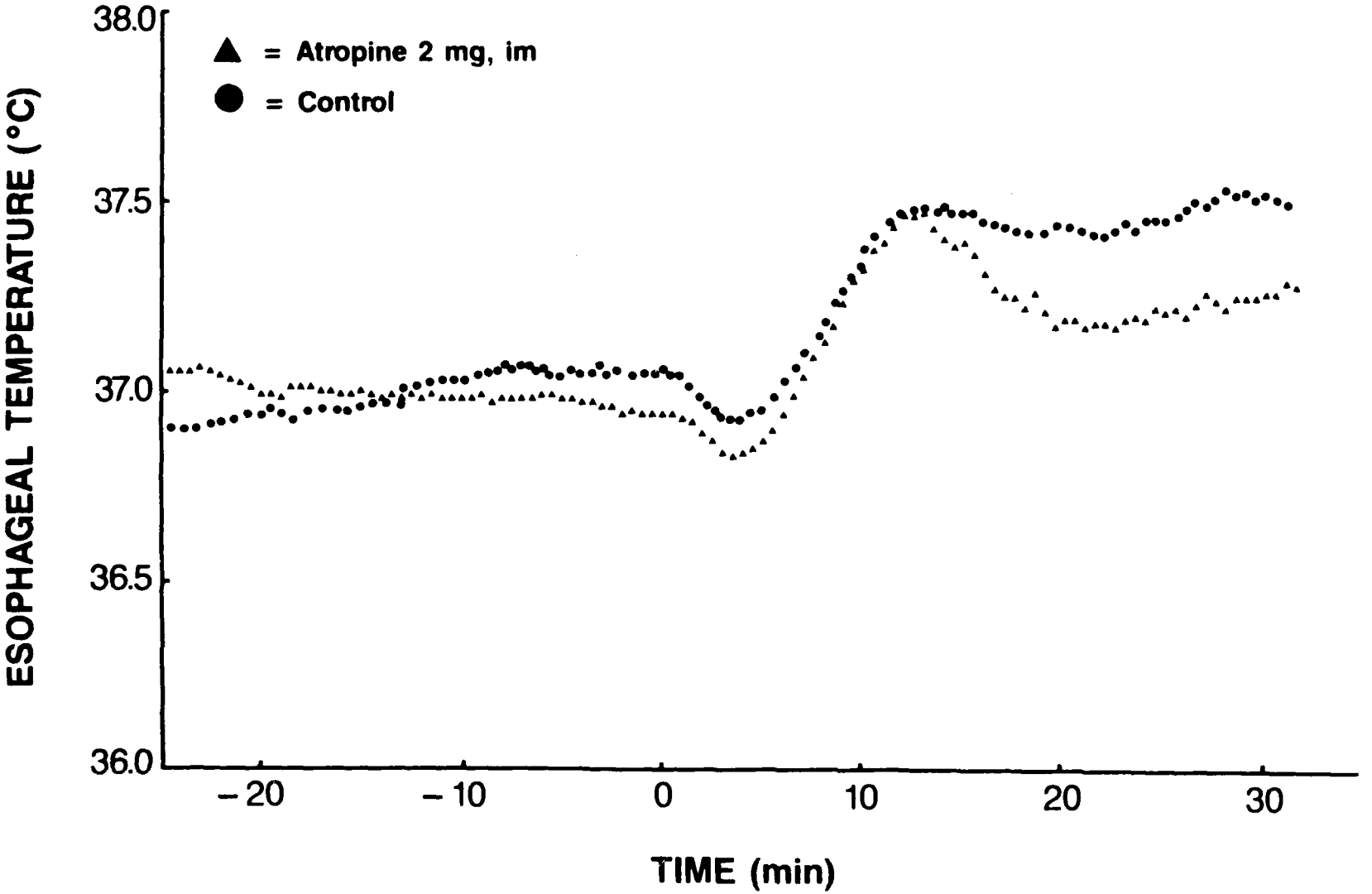
38.0
37.0
ATROPINE
CONTROL
0
20
40
60
80
TIME (MIN)


20.0
15.0
10.0
5.0
0.0
FBF
(ml·100ml⁻¹·min⁻¹)
Control
Atropine
30°C, 6.6 Torr
2mg Atropine Sulfate i.m.
55% VO₂ Peak
0
20
40
60
80
Injection
Exercise
Recovery
Time (min)


38.0
37.5
37.0
36.5
36.0
▲ = Atropine 2 mg, im
● = Control
ESOPHAGEAL TEMPERATURE (°C)
– 20
– 10
0
10
20
30
TIME (min)

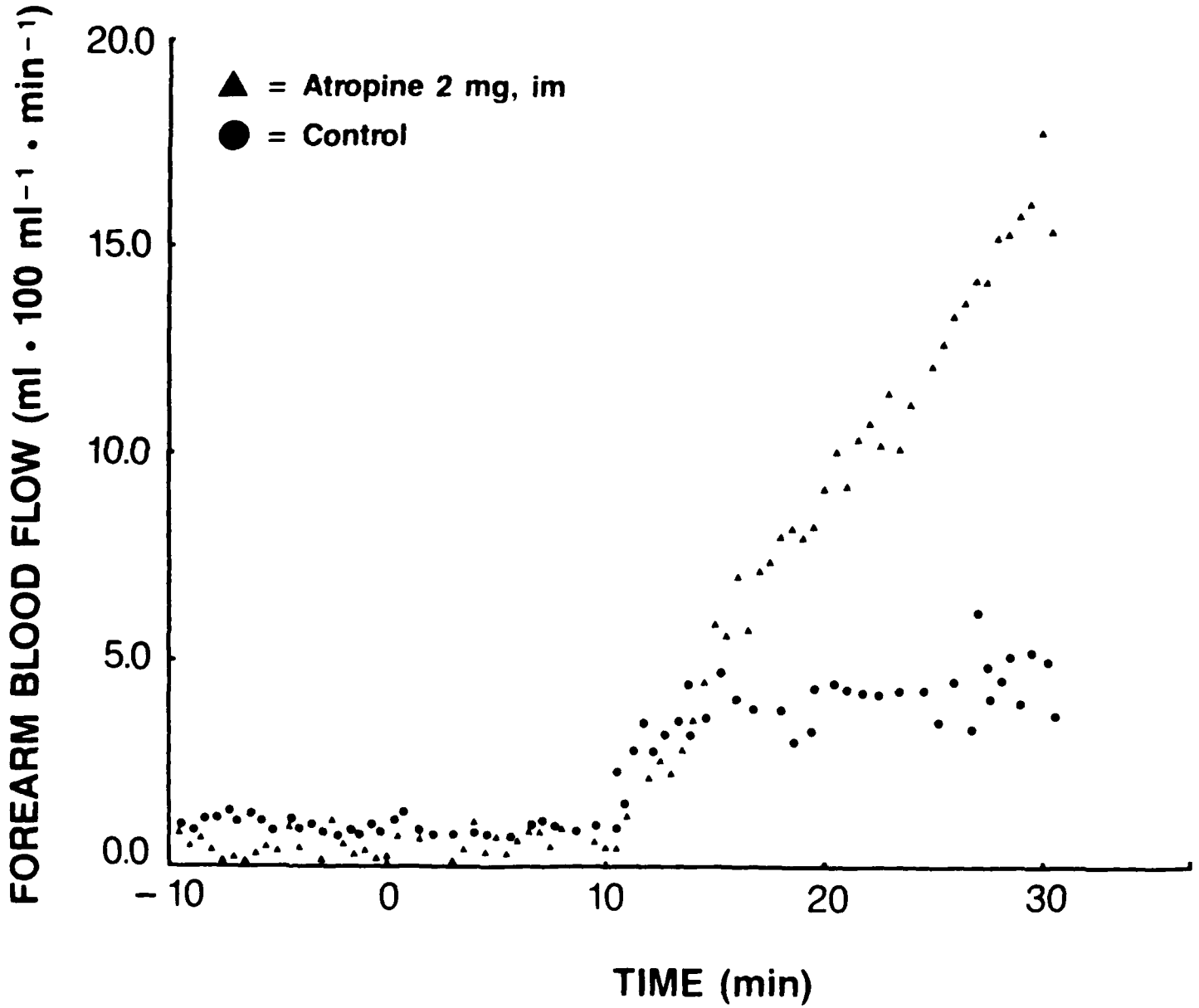

▲ = Atropine 2 mg, im
● = Control
FOREARM BLOOD FLOW (ml • 100 ml⁻¹ • min⁻¹)
20.0
15.0
10.0
5.0
0.0
– 10
0
10
20
30
TIME (min)

TABLE 4. INDIVIDUAL SLOPE AND T_{es} THRESHOLD (°C) FOR ARM SWEATING ($mg \cdot cm^{-2} \cdot min^{-1} \cdot {}^{o}C^{-1}$) AND FOREARM BLOOD FLOW ($ml \cdot 100ml^{-1} \cdot min^{-1} \cdot {}^{o}C^{-1}$) FOR SUBJECTS 1-4 DURING THE EXERCISE TRANSIENT AT 30°C.

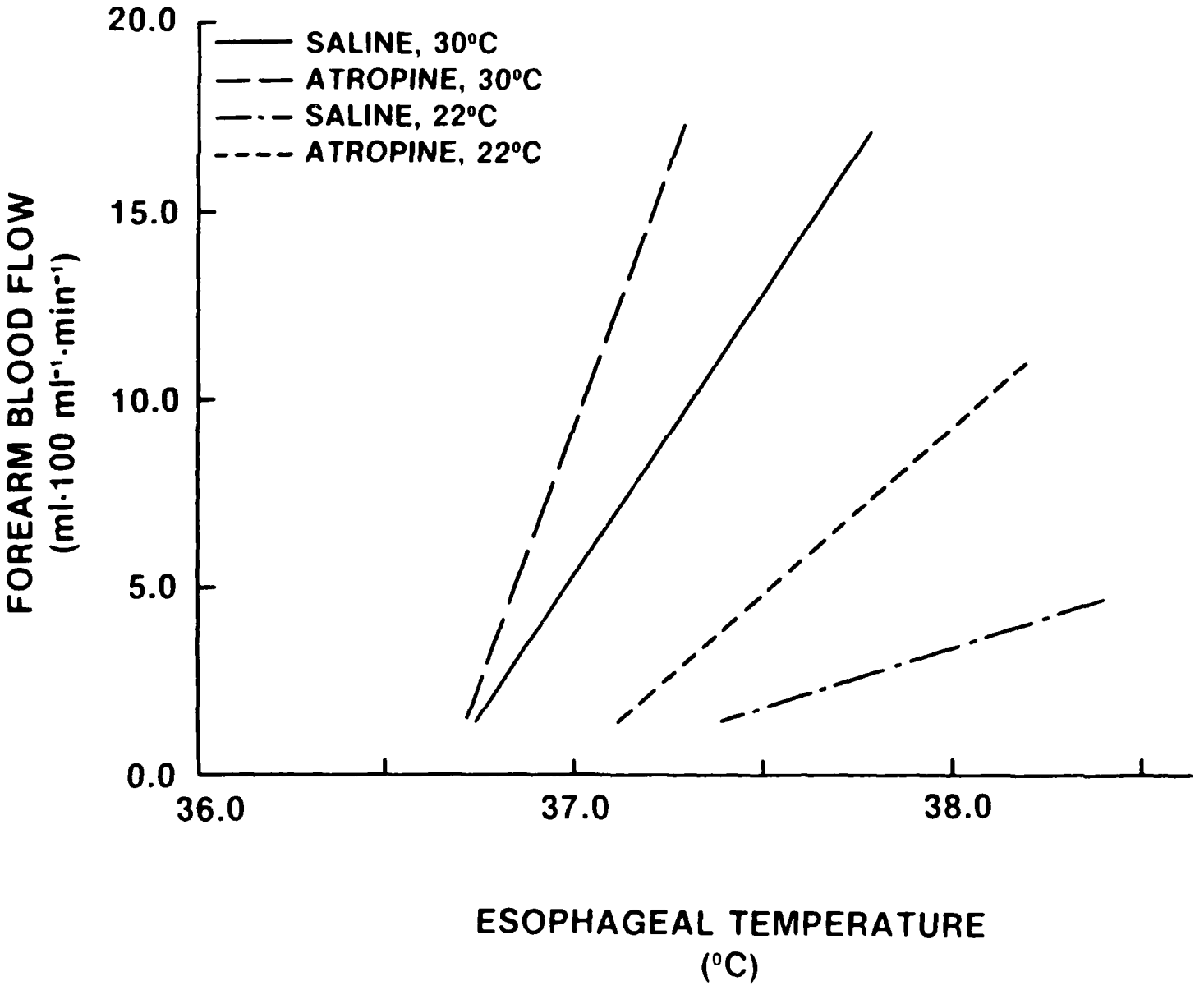
	$\dot{m}_s$ slope	$\dot{m}_s$ threshold	FBF slope	FBF threshold
SALINE				
1	1.31	36.78	18.90	36.92
2	0.82	36.37	7.17	36.14
3	0.84	36.26	13.00	36.86
4	1.38	36.54	21.00	37.09
$\bar{x}$	1.09	36.49	15.02	36.75
sd	(0.30)	(0.23)	(6.23)	(0.42)
ATROPINE				
1	1.18	36.81	25.39	36.67
2	0.82	36.51	26.50	36.54
3	0.75	36.85	26.90	36.80
4	0.45	37.06	32.10	36.90
$\bar{x}$	0.80	36.81*	27.72*	36.73
sd	(0.30)	(0.23)	(2.99)	(0.16)

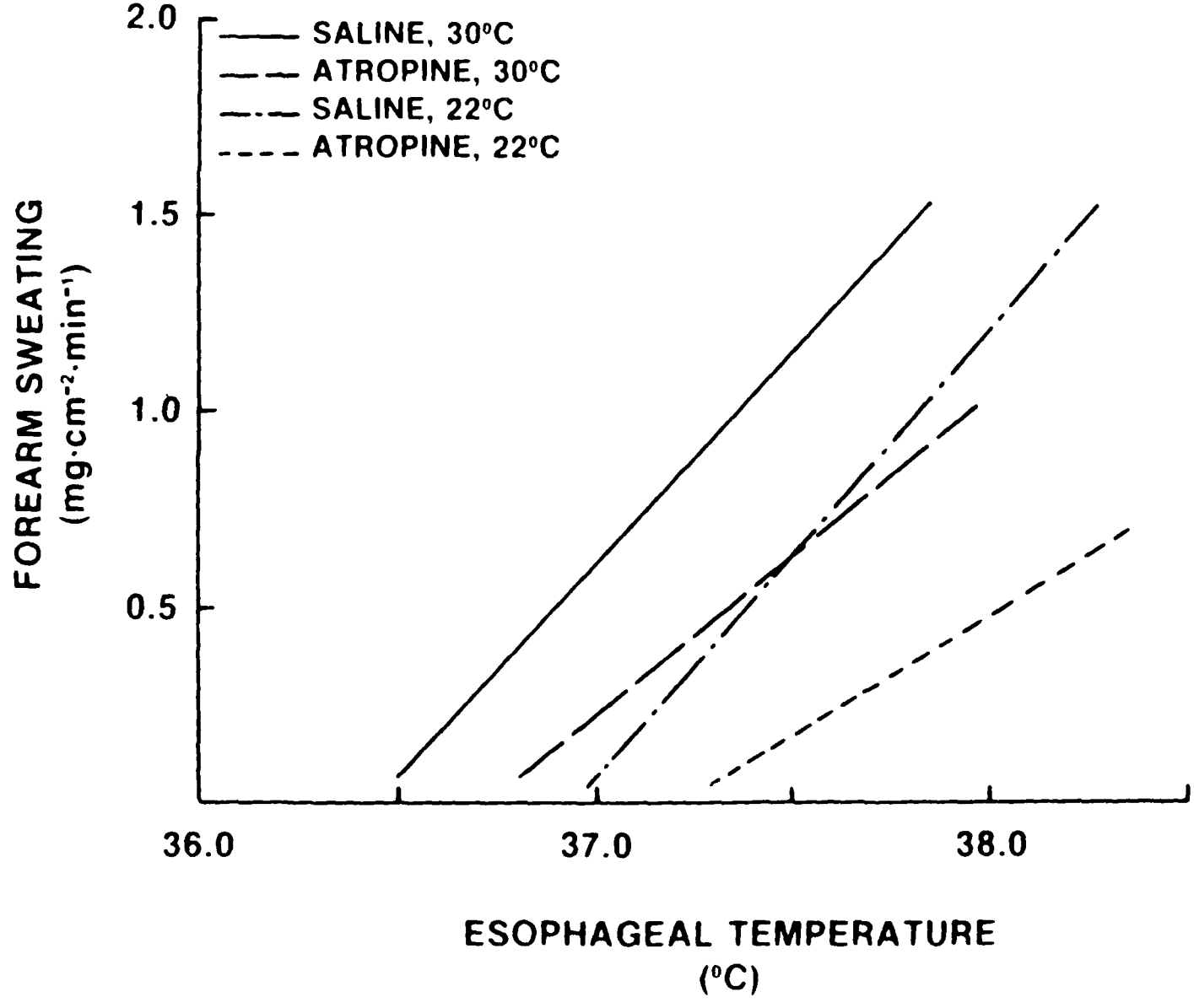
* $p < 0.05$, different from saline

TABLE 5. INDIVIDUAL SLOPE AND T_{es} THRESHOLD (°C) FOR ARM SWEATING ($mg \cdot cm^{-2} \cdot min^{-1} \cdot °C^{-1}$) AND FOREARM BLOOD FLOW ($ml \cdot 100ml^{-1} \cdot min^{-1} \cdot °C^{-1}$) FOR SUBJECTS 5-8 DURING THE EXERCISE TRANSIENT AT 22°C.

	$\dot{m}_s$ slope	$\dot{m}_s$ threshold	FBF slope	FBF threshold
SALINE				
5	0.94	36.8	1.03	37.3
6	1.25	36.8	1.92	37.2
7	1.09	37.0	2.90	37.5
8	1.25	37.2	3.33	37.4
$\bar{x}$	1.13	37.0	2.30	37.4
sd	(0.15)	(0.19)	(1.03)	(0.13)
ATROPINE				
5	0.62	37.1	7.25	37.2
6	1.26	37.1	8.19	37.1
7	0.46	37.3	10.23	37.3
8	0.25	37.5	9.36	36.6
$\bar{x}$	0.65	37.3*	8.76*	37.1
sd	(0.43)	(0.19)	(1.31)	(0.31)

* $p < 0.05$, *different from saline*


20.0
15.0
10.0
5.0
0.0
SALINE, 30°C
ATROPINE, 30°C
SALINE, 22°C
ATROPINE, 22°C
FOREARM BLOOD FLOW
(ml·100 ml⁻¹·min⁻¹)
36.0
37.0
38.0
ESOPHAGEAL TEMPERATURE
(°C)


2.0
1.5
1.0
0.5
SALINE, 30°C
ATROPINE, 30°C
SALINE, 22°C
ATROPINE, 22°C
FOREARM SWEATING
(mg·cm⁻²·min⁻¹)
36.0
37.0
38.0
ESOPHAGEAL TEMPERATURE
(°C)

An evaluation of how atropine affected thermoregulatory control is presented as the T_{es} threshold for sweating or vasodilatory onset and the slope of the linear regression equation of sweating to T_{es} and FBF to T_{es} in Tables 4 and 5 for the 30°C and 22°C environments, respectively. The similar responses of all subjects in atropine experiments, independent of environmental temperature is evident in this presentation. Specifically, there was a latency in the onset of forearm sweating compared to the placebo experiments which was coupled with a tendency for the suppresssion of the sensitivity of the relationship. Conversely, the onset of cutaneous blood flow occured at a lower temperature with an increased sensitivity. Hence in the 30°C environment, this enhanced cutaneous perfusion increased surface temperature and greater dry heat exchange occurred compared to the placebo experiments. At 20°C, this increased cutaneous perfusion greatly increases heat loss from the skin surface resulting in decreased core temperature even in the face of a relatively high endogenous heat production (~700 W or 390 $W \cdot m^{-2}$). The control of forearm blood flow during increasing esophageal temperature is shown in Figure 5 as the mean regression line for all of the subjects tested in a specific environment. For each pair of regression lines (either 30 or 22°C), treatment with atropine resulted in an increase in the slope or sensitivity of the regression line. These changes result in the increased forearm blood flow during steady-state exercise as shown in Tables 2 and 3. No change in the esophageal threshold for the onset of forearm vasodilation was apparent in the atropine experiments. In a similar manner the control of forearm sweating to changing esophageal temperature is shown in Figure 6. Again, the regression lines for each pair of experiments for a specific environment represent the mean response for the subjects. The consistent response after atropine treatment is a higher core temperature threshold for the initiation of sweating with no change in the slope or sensitivity of the

regression equation. Care must be taken to not rigorously compare the results from the two environments as the same subjects were not tested at both 22°C and 30°C. However, the response to atropine was similar in both environments.

DISCUSSION

The systemic administration of atropine sulfate in a volume equal to that contained in one field applicable auto-injector is sufficient to alter heat exchange in soldiers performing moderate exercise in a warm and in a cool environment. The self-administration of this anti-cholinergic agent without exposure to a nerve agent challenge may occur in field situations due to fear or confusion. A series of studies at numerous levels of environmental stress or thermoregulatory strain have been conducted by USARIEM to evaluate the effectiveness of a soldier's performance following this inappropriate or accidental atropine administration (7, 8, 10, 11, 13).

The current study has extended our observations of the effects of atropine on thermoregulation by including the direct assessment of the vasomotor and local sudomotor responses to the whole body sweating responses. During exercise in a 30°C environment, the depressed sweat secretion and subsequent decreased evaporative heat loss would have led to a large heat storage in the subjects thereby limiting exercise at that intensity. However, the increased blood flow to the skin surface increased the surface temperature and widened the thermal gradient between the skin and the ambient air providing for greatly enhanced dry heat loss from the subjects. This increase in cutaneous perfusion at 30°C compensated in part for the decrease in evaporative heat loss, and the subjects did not experience substantially large increases in heat storage, which would have interfered with the completion of the exercise bout.

In the cool environment, this increased cutaneous perfusion actually caused core temperature to decrease by 0.2°C after T_{es} had stabilized at approximately 10 minutes of exercise. The cutaneous vasodilation and the consonant dry heat loss seen in atropine treated subjects, in the absence of an anticholinergic nerve agent exposure, was sufficient to decrease body temperature. Further experiments will have to be done to more fully evaluate the implications of this increased convective and radiative heat loss in cold environments.

It is important to note here that the subjects were clothed in running shorts, shoes and socks to enable the appropriate measurements of heat exchange properties to occur. This is not the clothing that a soldier would wear in the field, however, in on-going studies at very low exercise levels, in soldiers dressed in BDU and MOPPIV configurations core temperature decreased over time at both 12°C (MOPPIV) and 22°C (BDU) after systemic atropine administration.

SUMMARY

1. The anticipated decrease in sweating and increase in heart rate occurred with the systemic administration of 2 mg of atropine sulfate.
2. Atropine caused widespread cutaneous vasodilation in healthy male subjects during moderate exercise in both a warm and a cool environment. This increased cutaneous perfusion is manifested in enhanced dry heat exchange in these environments.
3. During exercise in a cool environment, the increased cutaneous vasodilation is sufficient to lower the body temperature.

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